REMARKS

Claims 37-41, 46, and 49-62 are pending in this application. Claims 37-41, 46, and 49-62 have been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of the Claims Under 35 U.S.C. §103

Claims 37-41, 46 and 49-62 remain rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. (U.S. 6,228,401). Applicants respectfully traverse this rejection.

While the Advisory Action asserts that finality of the Office Action dated 1/12/2010 was proper because it was clear from reading the body of the rejection over James et al. that claim 41 was listed mistakenly in the heading of the rejection, Applicants respectfully assert that since the beginning of prosecution of this application, there has been an inconsistent listing of claims rejected over James et al. For example, in the non-final Office Action mailed August 11, 2009, the Office rejected "Claims 37-40, 46, and 49-6237-40, 42-43, 47-48, 50-62" over James et al. Applicants respectfully identified this error in the reply mailed October 10, 2009. Therefore, in so far as the final Office Action mailed January 12, 2010 provided a new listing of claims in the rejection over James et al., *i.e.*, "Claims 37-41, 46 and 49-62," Applicants were under the impression that the error in the Office Action mailed August 11, 2009 was corrected.

The goal of examination is to clearly articulate any rejection early in the prosecution process so that the applicant has the opportunity to provide evidence of

patentability and otherwise reply completely at the earliest opportunity. MPEP 706. However, contrary to the assertions in the Advisory Action, the claims rejected over James et al. have not been clearly identified during the entire prosecution of this Application. Indeed, Applicants have respectfully pointed out multiple errors and inconsistencies in the previous Office Actions, which demonstrate the failure of the Office to set forth a clear prosecution history record. Accordingly, in the event that the Office maintains the instant rejection, Applicants respectfully request, in the interests of compact prosecution and fairness to Applicants, that the Office clearly identifies the claims rejected over James et al. so that the application file history is complete (MPEP 707.07(f)).

With regard to the substance of this rejection under 35 U.S.C. 103(a), while it is the Office's position that the claimed product, with the particle size as recited in the claims, is obvious in view of the teachings of James et al., Applicants respectfully assert that the Office has not given proper weight to the whole of the teachings of this reference. Specifically, James et al. stresses the importance of particle size on the bioavailability of the relatively insoluble flutamide (col. 2, lines 17-20). James et al. indicate that flutamide compositions with X_{50} particle size values in the range of 5 μm to less than 26 μm exhibited increased bioavailability compared to those with an X_{50} of greater than 26 μm (col. 4, lines 43-55). James et al. conclude and explicitly claim that flutamide particles having an X_{50} of less than 26 μm, preferably in the range from about 5 to 20 μm, is a desirable characteristic to increase bioavailability (col. 2, lines 17-29 and claim 5).

Consistent with the teachings of James et al., the skilled artisan would reasonably conclude that increasing the X_{50} of flutamide particles to greater than 26 µm would decrease bioavailability. In so far as there would be no reasonable rationale for decreasing the bioavailability of a therapeutic drug, the skilled artisan would not be motivated by the explicit teachings of James et al. to make and use a flutamide particle having an X_{50} of greater than 26 µm as presently claimed.

In this respect, the instant case is analogous to *Ex parte Whalen*, 89 USPQ2d 1078 (BPAI 2008) (expanded panel). In this precedential opinion it was determined that a composition with a particular property at a high level (in this case viscosity) is not rendered obvious by a prior art reference that teaches a similar composition and suggests that the property be minimized, absent some reason to modify. Therefore, contrary to the Office's assertion, the instant feature of a flutamide particle having an X_{50} of greater than 26 µm cannot be rendered obvious by a reference that teaches the desirability of a flutamide particle having an X_{50} of less than 26 µm for increasing bioavailability. Indeed, there is nothing in the cited art that would give a skilled artisan even the slightest hint that an improved release rate of a flutamide particle having an X_{50} of greater than 26 µm could be achieved if unmilled flutamide is subjected to intensive mixing in a forced-action mixer with the at least one surface-active substance.

Furthermore, while the Office contends at pages 5 and 6 of the Advisory Action that Applicants have not provided any evidence of the difference of the claimed flutamide composition over the art and no comparison data, this

assertion is not accurate. A comparison of rates of release is presented on pages 16 and 17 of the specification as filed. Here it is clearly shown that with identical formulations (Examples 1, 2 and 4; Examples 5 and 6), the unmilled, intensively mixed formulation has a better release rate than the micronized (milled), non-intensively mixed formulation. Notably, the excipients present in Examples 4, 5 and 6 are the same as those disclosed in Example 7 of James et al. (both qualitatively and quantitatively). Thus, there could not be a clearer comparison to verify that intensive mixing of flutamide with a surface active substance has an influence on the particle size and bioavailability of flutamide resulting in unexpected improved properties of the claimed pharmaceutical formulation.

More particularly, as the comparison table on page 17 shows, formulations comprising unmilled flutamide, which has been intensively mixed with a surface active substance, have a significantly higher release rate than formulations comprising micronized flutamide that has not been intensively mixed. For example, the unmilled tablet of Example 1 has a release rate of 100%, while the micronized tablet of Example 2 exhibits a release rate of 71%. Notably, the ingredients of the formulations of Examples 1 and 2 are identical (both qualitatively and quantitatively). A skilled artisan would certainly recognize that it is very surprising that the unmilled composition has a quicker release rate, especially in view of the details the cited art teaches with respect to bioavailability.

Accordingly, in so far as the Office has failed to identify a reason to modify the composition of James et al.

to alter the X_{50} value of a flutamide particle to greater than 26 μm as presently claimed, Applicants respectfully submit that the Office has not established a *prima facie* case of obviousness. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

Regarding the rejection of claim 41 under 35 U.S.C. 103(a) as being unpatentable over James et al. in further view of Neri et al. (US 3,995,060), it is respectfully asserted that Applicants have established that base claim 37 is nonobvious in view of James et al. and therefore, claim 41, which depends from claim 37, is also nonobvious. It is therefore respectfully requested that these rejections under 35 U.S.C. 103(a) be reconsidered and withdrawn.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Advisory Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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